Non- Technical Abstract

The HER-2/neu (HER2) oncogene encodes a growth factor receptor protein that is involved in the unregulated growth of adenocarcinomas, which are the most common cancers in humans.. When the HER2 gene becomes amplified during cancer growth the HER2 protein becomes overexpressed on the surface of the cancer cells and those cells receive too many signals to grow and divide and, thus, become malignant. HER2 protein is also immunogenic in patients with HER2 overexpressing cancers; i.e. HER2 is a tumor antigen. That is, if a patient has a tumor which has "upregulated" the HER2 protein they may have developed an immune response against the protein. We know from investigations performed by several groups that the immune responses to HER2 in cancer patients are generally low level. Theoretically, if we could boost those immune responses to the level of the type of immunity one would see after a tetanus or flu shot, HER2 specific immunity may begin to have an effect in battling a patient's cancer. Vaccines have been designed immunize against HER2. These vaccines have been made of both proteins and fragments of proteins called peptides. HER2 specific vaccine trials performed in patients with cancer, using a variety of immunization methods, have resulted in several observations. First, cancer patients can be immunized against HER2 and boost HER2 specific immunity above those responses generated by virtue of exposure to a tumor expressing HER2. Secondly, after immunization against HER2, patients can begin to respond to other immunogenic proteins expressed by their tumors, a phenomenon called "epitope spreading". This broadening of the immune response during immunization is most likely due to the patient beginning to have a natural immune response at the site of the tumor in their body. Investigators believe that the phenomenon of epitope spreading is most likely mediated by very effective antigen presenting cells, termed dendritic cells (DC), initiating the immune response. Therefore, vaccine strategies that focus on stimulating these DC to initiate the immune response may be the most effective. Third, some vaccine strategies, such as using fragments of the immunogenic protein, peptides, require that patients be of a certain "immune system background" or HLA-type. Therefore, such vaccines may not be applicable to the majority of patients with a certain cancer. Finally, evaluating vaccine trials of HER in both mouse and man, the intracellular domain (ICD) portion of the protein appears to be the most immunogenic. In animals, vaccinating with the HER2 ICD can protect them from the development of cancer. We have made a HER2 ICD vaccine using plasmid DNA. A plasmid DNA vaccine is "naked" DNA and not attached to any virus or carrier to make it work. Our plasmid DNA vaccine encodes a portion of the HER2 gene, the ICD. Since the ICD is only a part of the entire HER2 gene, when given as a DNA vaccine, it is safe. The use of a plasmid DNA vaccine will allow the HER2 ICD to be transiently expressed in the skin, where we vaccinate patients, and generate an immune response in any patient regardless of their immune system type. Plasmid DNA vaccines have been tested in many animal model systems and even in humans and have been shown not to be very effective in eliciting immunity. The most likely reason for their lack of efficacy is that the vaccine is generally given in the muscle, which does not have any immune system cells in it to stimulate immunity. We have found that giving the vaccine in the skin along with a natural substance called granulocyte macrophage colony stimulating factor (GM-CSF) can result in the generation of significant HER2 specific immunity in mice. GM-CSF recruits skin DC, termed Langerhans cells (LC), and may result in LC taking up HER2 plasmid DNA and presenting the HER protein to the immune system. Thus, this vaccine strategy may allow the most important APC, DC, to be the initiating cells of the immune response. Another benefit of developing effective plasmid DNA vaccines is that they are inexpensive to make, stable for long periods of time, but most importantly, adaptable to immunization against multiple tumor antigens. Cancer is not cause just by one genetic alteration like HER2 gene amplification, but rather multiple genetic alterations. As we identify more important tumor antigens combination plasmid DNA vaccines can be formulated to immunize against multiple proteins that are involved in causing cancer to grow.

The aims of this clinical trial are to (1) determine the safety of a HER2 ICD plasmid based DNA vaccination in patients with advanced stage HER2 overexpressing breast and ovarian cancer, (2) determine the immunogenicity of a HER2 ICD plasmid based DNA vaccination, (3) determine if the dose of a HER2 ICD plasmid based DNA vaccine effects the development of an immune response, and, (4) determine whether intra and intermolecular epitope spreading occurs with HER2 ICD DNA immunization. The long-term goal will be to use this study as a platform to develop multi-antigen plasmid based vaccines for the prevention of common solid tumors.